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the difficult task of presenting an overview of the sizable literature about membrane channels and their potential involvement in disease. Furthermore, in numerous instances, the author summarizes how the genetic dysfunction has provided exciting insight into structure–function relationships key to normal channel activity.

Dr. Ashcroft has organized this book masterfully. The first five chapters provide an overview of pertinent background information including the basic properties of channels and the biophysical and molecular approaches commonly used to analyze channel function. This introductory information successfully provides the general reader with the vocabulary essential to understanding topics covered in later chapters without the burden of excessive detail. The remainder of the book is dedicated to discussions of selected ion channels and related topics. In most chapters, the basic properties of the channel(s) under discussion are highlighted, followed by a succinct summary of key structure–function studies, and a review of disease entities that can be attributed to alterations in this channel. Figures are appropriately intermingled throughout the text to reinforce salient points.

A significant portion of the book is dedicated to a discussion of voltage- and ligand-gated channels with identified mutations known to contribute to the development of specific diseases. As an example, the author describes that mutations that change the composition of voltage-gated sodium or potassium channels in cardiac muscle cause a lengthening of the ventricular action potential, increased calcium current, and early afterdepolarizations that initiate unwanted action potentials. These changes in membrane excitability result in long Q-T (LQT) syndrome, a rare cardiac disease that produces ventricular arrhythmia and potentially sudden death. This example is particularly important because it demonstrates that quite similar clinical phenotypes can be produced by mutations in different components of a single channel complex or by mutations in different channels within a common cell type. Also discussed are diseases such as hypokalaemic periodic paralysis, familial hemiplegic migraine and spinocerebellar ataxia type-6 that result from an altered composition (and consequent altered behavior) of voltage-gated calcium channels in skeletal muscle or CNS neurons. Mutations in voltage-gated chloride channels lead to the development of myotonia or depletion of extracellular volume and hypotension. Additional chapters focus on ligand-gated, receptor-channel complexes such as those gated by acetylcholine, glutamate, glycine, and GABA. Myasthenic syndromes are caused by mutations in skeletal muscle cholinergic receptors, and a rare form of epilepsy is attributed to a mutation in neuronal nicotinic receptor subunits. Many glutamate receptors exhibit marked calcium permeability, and overstimulation of these glutamate receptors is thought to be involved in a variety of neurodegenerative diseases or ischemic insults following a stroke. There is an extensive review of genetic mutations in chloride channels that cause altered function of epithelial cells in multiple tissues including the lung. These alterations underlie the etiology of cystic fibrosis, a very common and devastating disease in the United States and northern Europe.

Dr. Ashcroft's coverage of the subjects is not limited to commonly recognized classes of voltage- or ligand-gated channels, but instead includes the general properties and the potential clinical roles of a wide variety of membrane channels. In addition, later chapters cover channels in nonexcitable cells, especially those cells critical to the immune response. Information is included about pores formed by antibiotics in bacterial membranes and how these channel-like pores have been used as model systems to understand basic channel behavior. Also included is a discussion of parasite pore formation in intracellular membranes as a means to escape from phagosomes and how "channel forming" venoms may form calcium channels in mast cell membranes allowing calcium influx, degranulation, and release of histamine. Thus, the reader really can begin to appreciate the broad nature of "channelopathy" as a major contributor to the development of disease phenotypes.

In summary, Dr. Ashcroft has been very successful in meeting the stated task. The book is well written and enjoyable to read. Given the rapid advance of knowledge in this field, the content is amazingly up-to-date. This book is an excellent overview text for the advanced undergraduate or beginning graduate student and would be beneficial to the ion channel researcher as well as established scientists whose expertise is in unrelated areas. Furthermore, the author provides an excellent list of referenced books for those wishing a more detailed discussion of particular topics such as the biophysical properties of specific ion channels. I believe that this text also provides an excellent and essential source of information for clinicians wishing to better understand the relevance of "channelopathies" to the presentation of disease. Dr. Ashcroft has certainly hit the mark.

**Rodney L. Parsons**
Department of Anatomy and Neurobiology
College of Medicine
University of Vermont
Burlington, Vermont 05405

## The Direction of Cell Polarity

***Cell Polarity***
**Edited by David G. Drubin**
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Cellular asymmetry, or cell polarity, is integral to the development and functioning of all organisms from bacteria to humans. Modern methods have fueled tremendous advances in our understanding of the mechanisms underlying the generation of cell polarity. In recent years a number of reviews, including those contained in this collection, have captured and distilled the progress that has been made in a manner useful to both students and those already in the field. This collection acquaints the reader with the diversity of systems in which questions of cell polarity and organization are being tackled. The reviews progress from the simple to the complex, from bacteria to metazoans. Most reviews center around or-

ganisms or cell types: bacteria, yeasts, ciliates, epithelia, plant cells, *Xenopus*, and skin epithelia. Several are centered on themes: chemotaxis, exocytosis, and asymmetric cell division (yeast, *C. elegans*, *Drosophila*). For the most part, the reviews effectively get the reader up to speed on both background and recent developments.

As this collection attests, remarkable progress has been made. In systems such as budding yeast, it is now possible to trace a pathway from an initial spatial cue to the cytoskeleton (as reviewed in the chapter by Bähler and Peter, "Cell Polarity in Yeast"). For instance during mating, which requires chemotropic polarization toward a prospective partner, pheromone secreted by a cell of one mating type binds to a seven transmembrane receptor on the surface of a partner of the opposite mating type. Pheromone-bound receptor activates a G protein in a spatially restricted manner to release its $\beta\gamma$ subunit, which then recruits an adaptor protein Far1. Far1 in turn recruits Cdc24, the exchange factor for the Rho-type GTPase Cdc42. The resulting local activation of Cdc42 causes polarized assembly of the actin cytoskeleton, likely via the actin-related protein (ARP) complex. Five years ago, our mechanistic understanding of this polarization pathway and essentially all others was murky at best. This volumes describes the progress that has been made and prepares the reader to anticipate what is to come.

Although lacking molecular detail, the chapter by Frankel, "Cell Polarity in Ciliates," is an especially welcome inclusion given the fascinating contributions of work in ciliates to concepts of epigenetic inheritance. One particularly dramatic example is the stable inheritance of the ciliary row orientations on the surface of *Paramecium* and other ciliates. Vertical rows of ciliary units, parallel to the longitudinal axis of the cell, have a vectorial polarity because each ciliary unit is itself asymmetrical and points toward the anterior end of the cell. On occasion a perturbation gives rise to an inverted row (pointing toward the posterior). Row inversions can be stably propagated for thousands of cell divisions without any conventional genetic changes. Such stable inheritance occurs because new ciliary units are added to a template, the existing row, and because cytokinesis occurs perpendicular to the long axis of the rows thereby endowing each progeny with half of each existing row. Frankel's chapter compels the reader to consider the influence of epigenetic inheritance in other cellular systems where its manifestations may not be so obvious and is certainly worthwhile reading.

I also found particularly interesting a discussion of how shallow gradients might be reliably translated into axes of cell polarity in the review by Weiner, Servant, Parent, Devreotes, and Bourne ("Cell Polarity in response to chemoattractants"). How is a minute difference in the concentration of a chemoattractant across a cell transformed into an all-or-none axis? The authors reason that short-range positive feedback with long range inhibition must be built into the machinery (Turing, Bull. Math. Biol. *52*, 153–197, 1990; Gierer and Meinhardt, Kybernetik *12*, 30–39, 1972; Meinhardt and Gierer, J. Cell Sci. *13*, 321–346, 1974). They attempt to pinpoint the step in signaling at which this regulation might be occurring. This discussion highlights the broader challenge to reexamine the actual physiology of cells in the context of all of the emerging molecular information. Investigators will have to ask how (or whether) the molecular machinery, as known, can explain the sophisticated cellular behaviors observed.

Reading this collection of reviews brought to mind two general questions concerning cell polarity. To what extent is there a unifying theory of cell polarity? And what areas will see major advances in future years? Cell biologists are primed to expect conservation of mechanism. Perhaps this expectation was produced by the elucidation of cyclin-dependent kinase modules as the unifying theme in driving the eukaryotic cell cycle over a decade ago. Shall there be a unifying mechanism underlying the generation of cell polarity? To a certain extent, the answer to this question depends on ones initial bias and upon the stage of the process being considered. Cell polarity can be thought of in simple terms as the transmission of spatial cues, internal or external, to organize the cytoskeleton. Clearly the highest level of conservation is in the cytoskeleton; all eukaryotes contain actin and microtubule cytoskeletons. Even bacteria appear to rely on a structural protein FtsZ, which is distantly related to tubulin (Erickson, Cell *80*, 367–370, 1995). There appears to be less conservation in components in each step removed from the cytoskeleton. For the actin cytoskeleton, the actin-related protein (ARP) complex and Rho-type GTPases are conserved from yeast to humans. As one looks upstream from Rho type GTPases to the interface of signal transduction and spatial cues, much of the machinery is not conserved. For example, the Bud proteins that act as landmarks to direct patterns of polarization and division in yeast are not conserved in other eukaryotes. Far1 protein, the key link between G protein signaling and polarity establishment in yeast has no cognate homolog in higher cells. A conspicuous exception to this broad generalization is perhaps the seven transmembrane receptors as upstream transducers of a large number of chemotactic or chemotropic signals. Then again, these receptors impinge upon almost all aspects of cellular physiology. As a rough generalization, diverse spatial signals and landmarks act via regulatory networks, which converge on the conserved central machinery of the cytoskeleton.

Where is the richest frontier for examining the mechanisms of cell polarity and organization? Oddly enough, bacteria, the simplest of the systems examined in this volume, should witness the largest fundamental advances. Only recently has the field of prokaryotic cell biology emerged with the molecular organizations of bacteria being fully appreciated. However, we still know very little. Bacterial chromosomes separate as if driven by an active mechanism, but the basis of this movement is completely opaque (Gordon et al., Cell *90*, 1113–1121, 1997; Webb et al., Cell *88*, 667–674, 1997). Imagine eukaryotic cell biology without knowledge of the spindle. An excellent illustration of further surprises in store is the recent finding that regulators of bacterial cellular architecture exhibit extremely rapid dynamics. MinD, a regulatory protein that prevents division at the poles of *E. coli*, can be seen concentrated at one pole or the other of this rod-shaped bacterium. Amazingly, MinD localization appears to oscillate between poles every 20 s—this is unexpected to say the least (Raskin and de Boer, Proc. Natl. Acad. Sci. USA *96*, 4971–4976, 1999).

Like the movements of the MinD protein, rapid movements are occurring in the intellectual landscape of cell biology, and cell polarity is no exception. This volume is a snapshot of the field as it currently stands, and it whets our appetites for the advances sure to come in the next five years.

**John Chant**
Department of Molecular and Cellular Biology
Harvard University
7 Divinity Avenue
Cambridge, Massachusetts 02138

## Dogged Don

***Summon up the Blood: In Dogged Pursuit of the Blood Cell Regulators***
**By Donald Metcalf**
Miamisburg, OH: AlphaMed Press (2000). 214 pp. $29.95

Hematopoiesis is the process by which millions of mature blood cells, including erythrocytes, leukocytes, platelets and immune effector cells, are produced per hour by proliferation and differentiation of stem cells found in spleen, bone marrow, and fetal liver. It is in large part regulated by the action of the hematopoietic cytokines, some of which are found in the circulation, and most of which are also produced locally. A subset of four of these cytokines regulate the production of granulocytes and macrophages. These four cytokines are known as colony stimulating factors (CSFs) because of their ability to stimulate immature progenitor cells to proliferate and form colonies of mature cells in culture. For the last 35 years, Don Metcalf and his Unit in the Walter and Eliza Hall Institute of Medical Research have made a major contribution to our understanding of the nature and actions of the CSFs. *Summon up the Blood* is a strongly autobiographical, personal account of the development of this field from one of its most eminent leaders. The book covers the identification and purification of CSFs, the cloning of the genes encoding them, analysis of their biological activities and roles in disease, the identification of their receptors, and the effects of inactivation of their genes in mice. During this period two important advances were necessary for these achievements. The first was the development of sensitive protein microsequencing required to sequence the very small amounts of purified CSF protein available. The second was the development of recombinant DNA technology that enabled production of the large amounts of CSF protein needed for biological testing and eventual therapeutic use.

Following completion of his medical degree at Sydney University, in 1954 Don Metcalf was appointed Cardin Fellow in Cancer Research at the Hall Institute in Melbourne. He and two outstanding fellow medical graduates, Jacques Miller and Gus Nossal, joined the Institute at about the same time; they were attracted there by MacFarlane Burnet, who in 1960 won the Nobel Prize for his work on acquired immunological tolerance. From 1965 to 1996, the period covered by the book, Don Metcalf was Head of the Cancer Research Unit and Assistant Director of the Institute, which was headed during this period by Gus Nossal. The focus of Metcalf's Unit on the developing area of hematopoiesis differed from the overall focus of the Institute which was the burgeoning field of immunology. In his positions at the Hall Institute, Don was able to attract some of the best young research colleagues Australia had to offer, several of whom continued to work with him as more senior scientists and currently hold important positions in Australian biological science. Over his prolific research career, Metcalf has published more than 400 peer-reviewed scientific papers, 200 other scientific papers, and 7 books. He has received numerous honors and awards.

The book begins by describing how in 1964, Ray Bradley introduced Don to the method for growing bone marrow colonies. Bradley, working in the Physiology Department of the University of Melbourne, had developed the method completely independently of Pluznik and Sachs at the Weizmann Institute in Israel. Based on his frustration with whole animal studies of thymus development, Don saw the potential of using in vitro approaches, and decided to establish these cultures in his own laboratory. After working for a year with Bill Robinson, his first Ph.D. student, Don left for a sabbatical year in the U.S. At this stage, I arrived to commence my Ph.D. project on the characterization of CSF.

The chapter entitled "The Dubious Joys of Bioassays," describes an activity I remember Don spending much of his time doing on return from his sabbatical—counting colonies. He would sit bolt-upright in a straight-backed chair (due to perennial back problems), smoking short cigarillos. We had many conversations where his eyes did not leave the scope! He is justifiably proud of assuming the burden of colony counting over the decades. His fascination and dedication to thoroughly analyzing cultures, and to identifying the cell types in colonies stimulated by biologically active fractions, was critical to the discovery of granulocyte-macrophage CSF (GM-CSF) and in particular, of granulocyte CSF (G-CSF), which stimulates the formation of very small, transient colonies, that others might have missed or ignored.

The description of the early period covers the characterization of CSF in mouse serum, its discovery in human urine and its purification from this source. This CSF was subsequently named macrophage CSF (M-CSF) by the Metcalf group. Following its distinction from other CSFs by competitive binding assays, I named it CSF-1, on the basis of the subsequently verified prediction of its action on cells other than macrophages and not because, as indicated in the book, it was the first CSF to be purified. In the current literature, both names persist. While I prefer CSF-1, in this article M-CSF is used, as in the book. The task of purification of the CSFs (M-CSF, GM-CSF, G-CSF and interleukin-3 [IL-3 or multi-CSF]) was immense. In contrast to two previously purified growth factors, epidermal growth factor and nerve growth factor, which are unglycosylated proteins representing up to 1/40 of the starting material, the CSFs are glycoproteins, representing as little as 1/100,000 of the starting protein. Initially, the goal of CSF purification was to obtain purified factor for in vivo experiments. After the recombinant DNA revolution, the immediate aim was to